

# NEMATODES, NERVOUS DISEASE, AND NEUROTROPIC VIRUS INFECTION

## OBSERVATIONS IN ANIMAL PATHOLOGY OF PROBABLE SIGNIFICANCE IN MEDICAL NEUROLOGY

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Beautyman and Woolf (1951) dealt with observations on a child in whom an ascaris larva was found in the brain along with acute poliomyelitis of the brain-stem. These findings might be important for the reasons given by them—namely, that the worm might have facilitated the virus infection, or that there might be a complex virus-helminth relationship as exemplified by the work of Shope (1943) on swine influenza, virus infection being interdependent on the lung-worm and the earthworm. Another point is that there were no neurological signs referable to the larval thalamic lesion, but that neural larval migration might result in occasional cases of focal and generalized epilepsy. They referred to the paucity of pathological reports on nematode invasion of the nervous system of man, but some relevant studies on veterinary pathology inadvertently received no comment. For obvious reasons it usually takes a long time before work in the latter category receives medical notice—inaccessibility of veterinary journals playing some part. Yet examples could be given in which studies on animal diseases were the starting-point in the identification of analogous human disorders. A classic example might be the observation by Griffith Evans (1880) that a trypanosome caused surra of horses in India; Ronald Ross admitted a debt to that work in his famous monograph on malaria, and it must have influenced Bruce, Dutton, and Castellani in the later work on African trypanosomiasis in animals and man.

### Epizootic Cerebrospinal Nematodiasis

Initially, we deal with a specific nervous disease of animals which has occurred as a seasonal epizootic in the Orient, and which is caused by immature nematodes (*Setaria digitata*). Great credit for this contribution must be given to Japanese workers. For full accounts of the disease—now called by us epizootic cerebrospinal nematodiasis—with all appropriate Japanese literature, see Shoho (1952), Innes, Shoho, and Piliat (1952), and Innes and Shoho (1952); another paper by Innes (1951) dealt specifically with the same disease in goats in Ceylon.

This epizootic neuroparalysis has occurred in domestic animals in Japan, Korea, and Ceylon for many years. It is not an uncommon disorder, and it is not one in which nematodes on rare occasions accidentally wander into the nervous system. Indeed, we contend that, if Japanese B encephalitis deserves the title "epidemic," then animal nematodiasis should be preceded by the word "epizootic." It occurs in the summer and autumn, coinciding with the insect vector season. The animals suffer from an acute or

subacute paralysis of all four limbs or only the hind limbs, and this is unaccompanied by constitutional signs. Some die quickly, others linger a few weeks, and some recover with residual neurological defects, and in view of what is known about the pathology all these clinical variations are understandable.

The essential pathological process is that of a focal encephalomyelomalacia, which in many cases proceeds within a few days to liquefaction and cavitation. The latter may be only microscopic, but one of us (C.S.) has also seen gross cavities. The lesion may be single or there may be a few, but rarely are there disseminated lesions. The focal process may attack any part of the nervous system in a seemingly haphazard manner. Haemorrhage is inconstant, for this would depend on the migrating nematode striking vessels; hence the lesion itself, wandering in a tortuous microscopic path, might be difficult to detect macroscopically. In several goats from Ceylon the whole nervous system was embedded for section-cutting—in the cord, transverse cuts alternating with longitudinal ones. This indicates the possibly arduous nature of pathological examination which might be required for identification of the disease (Beautyman and Woolf found no naked-eye changes indicative of larval infestation). Meningeal infiltrations with many eosinophils may be seen, sometimes extending to areas far from the malacic site: random selection of nervous tissue for sections might thus foster the idea that only an eosinophilic/lymphocytic meningitis was present. The total lesion is unlike that found in any viral, bacterial, protozoal, mycotic, toxic, or deficiency disease; nor is it demyelination, for all structures rapidly disintegrate in the centre. The process is an acute malacia in a restricted track followed by secondary degeneration of nerve-fibre tracts, and the gigantic swellings of axis cylinders (Wallerian degeneration) in, around, above, and below the malacia are a predominant feature. These findings are unmistakably diagnostic, and are consistent with our concept that the process is simply a mechanical traumatic effect of a wandering worm—now proved experimentally.

It was proved by Japanese workers that the animal neuroparalysis in Korea and Japan was caused by young worms (*Setaria digitata*). This finding was based on the association of worms with lesions, and later by experimental production of the disease in sheep, goats, and horses. The aetiological concept was first suggested by Fujita, and amplified and proved experimentally by Niimi and Kimura (1939-43) and 28 others. A full account is available in a five-volume Report of a Special Research Commission (1939-43), but unfortunately an English translation is not available. Our other papers summarize all these studies, while in the caprine paralysis in Ceylon, McGaughey (1951)—at our instigation—subsequently demonstrated the causal setaria. The name given now is appropriate—namely, epizootic cerebrospinal nematodiasis—for it is better than the original Japanese label of setariasis, and we think other filaria or immature nematodes might be involved in production of the same pathology in the same or different species. The natural host of *Setaria digitata* is cattle, in which the adults reside in the abdominal cavity without any visible pathological effect, and in which species microfilariae finally enter the blood.

In the Orient the vectors of the worm are mosquitoes, and the very same species are listed as vectors of Japanese B encephalitis. The microfilariae, on being taken up by the insects, mature in about 14 days as infective larvae, which on passage into *unnatural hosts* (sheep, goats, and horses) migrate by direct routes to the nervous system, and therein produce the damage described. The difficulties of determining the helminthic cause are significant. *Setariae*, like all filariae, are notorious wanderers, and in affected animals, having produced a lesion, may straggle away and be found not in the nervous tissue but in the cerebrospinal fluid. It may also be impossible to recognize parasites in the nervous system of animals with a chronic history of paralysis; for, apart from their wandering, they may dis-

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integrate or calcify, or only remnants of a hyaline capsule may be found. Moreover, if a lesion is not detected macroscopically, the nervous system, even of the sheep or the goat, is a big organ in which to find a small worm.

We now turn to observations by Beautyman and Woolf, and how these cut across the paths of those in animal pathology.

#### Clinically Inapparent, or Masked, Helminthic Infection of the Nervous System

This phenomenon (Beautyman and Woolf) is supported by observations on nematodiasis. As the malacic lesion is approximately the same size (whether in sheep, goats, or horses) it is clear that clinical signs might depend primarily on the neuro-anatomical location of the focus. In animals with a voluminous nervous system (and enormous length of cord), as in the horse, however, few or no nervous signs might eventuate if the lesion was located in some parts of the cerebral cortex or lower lumbar region of the cord; a minor degree of neurological upset might, indeed, never be spotted. The malacic lesion must be the immediate reaction; a granulomatous one might be the residual, more chronic, effect, in which the parasite might be dead. Consequently, unless the paralysis was immediately fatal, neither the malacic lesion nor the parasite might be recognizable in animals (or man) if life was prolonged. Tanaka *et al.* (1945), in a pathological survey of the brains of 100 old horses, found lesions with and without parasites in nine animals in which no clinical signs were seen during life. This same problem of clinically inapparent disease in the presence of even disseminated encephalitic lesions in lower animals has been raised also in experimental allergic encephalitis in mice by Olitsky *et al.* (1950), in guinea-pigs by Lumsden (1949), and by personal observations. The most careful neuropathological examination in such animal conditions thus becomes almost imperative.

#### Nematode Infestation Facilitating Virus Invasion of the Nervous System

So far as neurotropic virus infections are concerned this problem has not been seriously considered. Shope (1943), however, opened the way by his fascinating work proving that the complex pathogenesis of swine influenza was bound up with earthworm, lung-worm, virus, and *Haemophilus suis*. (See also the work of Syverton *et al.* (1947) on the association of *Trichinella spiralis* and lymphocytic choriomeningitis in guinea-pigs.) Our speculations on a possible parallel adjacency between *Setaria digitata* (and the disease) and Japanese B virus encephalitis are no more flights of fancy than those of Beautyman and Woolf. Sabin, Ginder, and Matumoto (1947), in a study of the epidemiology of Japanese B encephalitis, indicated that the virus was sometimes spread extensively in domestic animals in endemic regions of Japan when human beings were affected very little. The problem of how the virus maintains itself in nature during non-epidemic years was considered of profound significance, and they raised the question of intermediate arthropod and helminthic hosts, but without specification. The same mosquitoes have been incriminated in the transmission of Japanese B encephalitis and in nematodiasis of animals, hence an interrelationship cannot be dismissed lightly.\*

#### Dual Neurotropic Virus and Helminthic Infections

If a helminth lodges in the nervous system the final outcome will depend partly on its neuro-anatomical location, and perhaps partly on survival of the worm to continue its damage. That neurological signs can be masked by a later

or simultaneous virus infection has been proved by Beautyman and Woolf. In a routine pathological examination of the brains of 69 horses naturally infected with Japanese B (equine) encephalitis, Sugawa, Mochizuki, and Yamamoto (1949) found a malacic lesion with and without setaria in four cases. Consequently, we might ask how often this has happened before: if clinical and other evidence pointed to virus encephalitis, then presumably little further study would be made of the cases but to keep nematodiasis in mind; yet that condition might be of significance. We believe that in Japan neural nematodiasis of animals has often been confused with virus encephalitis, particularly if too much reliance is placed on clinical data and even on neutralization tests. The latter could be positive in the presence of a coincidental nematodiasis; or, indeed, the virus infection might be facilitated through this. It is thus interesting to find, in some reports on the pathology of human Japanese B encephalitis, mention of "mushy areas" in the spinal cord, but it is not certain that these foci received specific histological study. Further, one of us (C.S.) has observed cavitation in the brains of four children reputed to have died from Japanese B encephalitis—a finding which points to the existence of some coincidental process, or an as yet undescribed pathological feature of Japanese B encephalitis.

#### Migratory Paths of Helminths to the Central Nervous System

Beautyman and Woolf discuss this with particular reference to the classical work of Yokogawa (1923) on ascaris, and therefore emphasis is laid on intravascular paths. It is generally accepted that ascarids, after the hatching of the eggs in the intestines, go on a tour to the lungs and that some larvae may wander into the general circulation and reach the nervous system or the eyes. Yokogawa's original experimental findings, in which 10 out of 14 mice (given a large number of canine ascaris eggs) showed haemorrhages of the cerebrum due to migrating larvae, were also interpreted to mean that the route was via the circulation. We wonder why a direct pathway cannot be considered to account for all such cases.\* In cerebrospinal nematodiasis it can hardly be questioned that the direct tissue path is the one taken by setariae, for the malacic lesion is not embolic in nature but mechanically traumatic. We might draw attention here to some obscure work by von Brand and Cullinan (1943), who showed that strongylid larvae of fish, when transplanted into unnatural hosts (rats and chickens), invaded the nervous system and paralysed and killed the latter. These larvae took the direct route, for one could trace the histological path through connective and muscle tissue, and between vertebral joints to the cord, revealed by the granulomatous eosinophilic tissue reaction. The problem of what parasites do in unnatural, as compared with natural, hosts might be the crux of many problems. The thesis that the nervous system (and eye perhaps) may be a strange anatomical site of attraction in unnatural hosts receives further support from Tiner (1951), who reported 100% mortality in white mice from damage to the brain, following infection by ascarids derived from racoons.

#### Possibility of an Analogous Cerebrospinal Nematodiasis of Animals Occurring in Man

This has been covered fully in another paper (Innes and Shoho, 1952), but the brief explanations given show how such a disorder could evade both accurate clinical and pathological detection—in fact, if patients lived diagnosis might be impossible. Skin and complement-fixation tests, using setaria antigen, might, however, be usefully employed. There are many reports in medical literature reminiscent of the animal disease, grouped under such vague headings as

\*The fact that a nematode, and its lesion, are found in one part of the nervous system and evidence of virus infection is found in another would not necessarily exclude a connexion. A nematode could act as a destroyer of the blood-brain barrier in one region and thus facilitate virus invasion, and then wander out and away and penetrate another region when a stage of viraemia was over.

\*Reference has been made to the occasional need for a far more careful neuropathological examination than that made in a routine pathological survey of the nervous system. In the case of Beautyman and Woolf, for example, it would have been of the greatest interest to know whether the nematodal lesion in the thalamus was linked to the pia mater by a connected or disconnected glial scar track.

subacute necrotizing myelitis, asymmetrical haemorrhagic encephalopathy, degenerative softening, and so on. We especially draw attention to reports of eosinophilic meningitis with focal malacia—with clinical acute paralytic signs (or those of transverse myelopathy) and a complete absence of evidence indicative of cause (virus, bacteria, or any other—but helminths never considered). It is even conceivable that some cases of reputed disseminated sclerosis, with predominant spinal signs, which do not progress after a primary paralytic attack could be of this nature. A study of the reported data in veterinary pathology might conceivably help to a better understanding. The observation of asymmetrical cerebral cavitation (caused by nematodes?) in newborn and young calves by one of us (C.S.) might raise speculations in other directions; for multicystic degeneration in the brain of newborn and young children, of unestablished cause, is adequately dealt with in neuropathological literature.

### Conclusion

Finally, some indirect support for our ideas arises from Wilder's (1950) work on human endophthalmitis. In 46 eyes of children and adolescents, received from many parts of the U.S.A., a variety of original diagnoses had been made; all showed some features of an eosinophilic or granulomatous lesion, but in none of the original sections were worms present. Serial sections (in one eye—2,300 slides) revealed the finding of a larva in 24 eyes, and the changes were so uniform in type that a diagnosis of nematode endophthalmitis was made for all 46. This disease has an exact analogy in an ocular disease of horses in India, known almost from antiquity, and is caused by *Setaria (digitata?)*; peculiarly enough, it is sometimes associated with paraplegia (Kumri), which we think is cerebrospinal nematodiasis. Perhaps such human helminthic ocular lesions are no more than an extension in sequence and location of intracranio-vertebral nematodiasis—that is, helminthic parasites can enter the eye via the cranial cavity. In Japan, ocular filariasis in horses is also common, and is also caused by *Setaria digitata* (see Kume, 1951), but onset is about a month later in the year than that of the nervous disease, and both may occur together. This same probability might be remembered in human medicine.

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A note in the *Royal Army Medical Corps News* reports that Sir Almroth Wright's work at the Royal Victoria Hospital, Netley, has been commemorated by the erection of a plaque in the main hall of the hospital. Sir Almroth was at one time professor of pathology in the Army Medical School, and made the first trials of anti-typhoid inoculation on himself and the surgeons on probation in the laboratory of the hospital between 1895 and 1898.

## HEREDITARY METHAEMOGLOBINAEMIC CYANOSIS

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The increased interest in heart surgery, as introduced by Tousin, Gross, Blalock, d'Allaines, Bonzelot, Lenègre, Soulie, Karayannopoulos, Tountas, Karageorges, and Papanicolis, has drawn attention to the problem of cyanosis as a whole, and not merely as a symptom of congenital malformation of the heart. In a series of investigations of the various cyanotic conditions which I have been carrying on with my associates, Drs. Loucatos and Loutsides, since 1946 (Codounis, Loucatos, and Loutsides, 1947, 1948; Codounis, 1948, 1949), a morbid autonomous entity of the red corpuscle has been defined which we have called "hereditary methaemoglobinaemic cyanosis" (H.M.C.) and which has been increasingly attracting medical attention.

Since 1844, when François described the first Belgian cases of cyanosis without cardiopathy, only 19 similar cases had been noted in the literature up to 1945 by Sievers and Ryon, including their one case and the two of Lian and his co-workers. With the addition of single cases by Graybiel *et al.* and Barcroft and his associates, the total recorded cases of this kind of cyanosis was raised to 21 by the end of 1945.

In 1946 we added our 14 cases of the Vaftochilary family (Chart 1), demonstrating definitely for the first time the hereditary mode of transmission of congenital and familial methaemoglobinaemic cyanosis. At the same time we completed the study of its clinical, biological, and therapeutic aspects. Confirmation of our conclusions has come from Bensis, Gouttas, Pyrras, and Vacrinos (Athens Medical Society, 1947); King, White, and Gilchrist (1947); Gibson and Harrison (1947), who published five cases in a family of nine; and Lutembacher (1949), who found six similar cyanotic cases in four generations of one family. A case has also been reported by Fisher and Wide Price (1949).

Having had occasion during the last two years to study a new genealogical tree comprising 85 members who lived throughout Southern Greece, including 10 born cyanotics, I thought it might be of interest to present this study with a summary of our investigations as a whole. I hope that this research will adequately elucidate this genotypic disease of the blood and differentiate it from other cyanotic conditions.

### A New Family Tree

In the study of our second family tree (Chart 2), the Melaniarides (a nickname given the family by people of the district who were impressed by their unusual colouring: *melani*, ink; *vafo*, colouring; *helos*, lips) we followed the system used in that of the Vaftochilary family. Convinced after a series of clinico-biological tests that the two cyanotic sisters—Nos. 7 and 8 of this tree—who came to see us in October, 1949, with a diagnosis of congenital heart disease were actually H.M.C. cases, we thought it wise to undertake a special investigation in order to reach 85 members of the different families of this tree spread over a number of